Trends in Neuroscience and Education 10 (2018) 19–29

Contents lists available at ScienceDirect

Trends in Neuroscience and Education

journal homepage: www.elsevier.com/locate/tine

Short-term cognitive training recapitulates hippocampal functional changes associated with one year of longitudinal skill development

Miriam Rosenberg-Lee[a,b,c,*], Teresa Iuculano[a], Se Ri Bae[a], Jennifer Richardson[a], Shaozheng Qin[a], Dietsje Jolles[a,d], Vinod Menon[a,b,e,*]

[a] *Department of Psychiatry & Behavioral Sciences Stanford University School of Medicine, Stanford, CA 94304, United States*
[b] *Stanford Neuroscience Institute, Stanford University School of Medicine, Stanford, CA 94304, United States*
[c] *Department of Psychology, Rutgers University, Newark, NJ 07102, United States*
[d] *Education and Child Studies, Leiden University, Wassenaarseweg 52, 2333 AK Leiden, The Netherlands*
[e] *Program in Neuroscience, Stanford University School of Medicine, Stanford, CA 94304, United States*

A B S T R A C T

A goal of developmental cognitive neuroscience is to uncover brain mechanisms underlying successful learning. While longitudinal studies capture brain changes following 'schooling as usual', short-term training studies can more directly link learning to brain changes. We investigated whether eight weeks of cognitive training recapitulates longitudinal changes in hippocampal engagement and connectivity. Nineteen children underwent a training program focused on improving arithmetic skills, along with fifteen children in a no-contact control group. Before and after training, or no-contact, both groups performed an arithmetic task during neuroimaging and a strategy assessment. Training increased activity in the anterior hippocampus, and gains in memory-based strategies were associated with decreased lateral fronto-parietal activity and increased hippocampus-parietal connectivity. No changes were observed in the no-contact control group. Our results demonstrate that short-term training can recapitulate long-term neurodevelopmental changes accompanying learning and identifies plasticity of hippocampal responses as a common locus of cognitive skill development in children.

1. Introduction

A fundamental goal of developmental cognitive neuroscience is to determine brain mechanisms underlying successful learning. However, disentangling the effects of experience and maturation on brain development is especially difficult when investigating the neural basis of academic skill learning. While longitudinal designs provide insights into brain plasticity mechanisms that accompany increasing mastery of academic skills, they cannot determine if the observed neural changes are directly related to educational experiences or whether they reflect ongoing brain maturation. Tightly constrained, well-controlled, short-term training studies are necessary for complementing longitudinal studies and assessing learning in a more precise manner.

Here we focus on the development of math skills, and in particular on math fact learning, a foundational capacity for higher mathematics and a hallmark of cognitive development [1]. Behaviorally, math fact learning is characterized by shifts in cognitive strategies from laborious counting to retrieval from memory [2–4]. Recent research has identified a developmentally-specific role of the medial temporal lobe in this gradual transition between cognitive strategies. Specifically, converging evidence from multiple experimental paradigms point to the importance of the medial temporal lobe, and particularly the hippocampus, during the development of math facts retrieval in elementary school children [5–8,16]. Yet none of these studies have explicitly manipulated learning experiences to test the functional relevance of this brain structure in the development of successful math fact retrieval. Here, we investigate whether eight weeks of an intense arithmetic training, focused on promoting efficient strategies and speeded practice for arithmetic problem solving [9,10] is accompanied by brain plasticity in hippocampal activity and connectivity.

The first studies to examine the neural correlates of arithmetic fact retrieval capitalized on differing retrieval rates between arithmetic operations [11–13]. In elementary school children, addition, relative to subtraction, is more often solved by retrieval [14,15] and two neuroimaging studies have found greater hippocampal activity during addition compared to subtraction problem solving in this age range [8,16]. This pattern of results stands in stark contrast with studies in adults, where retrieval rates also differ between operations [17], but

* Corresponding authors at: Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94304, United States.
E-mail addresses: miriam.rosenberglee@rutgers.edu (M. Rosenberg-Lee), menon@stanford.edu (V. Menon).

https://doi.org/10.1016/j.tine.2017.12.001
Received 19 June 2017; Received in revised form 15 December 2017; Accepted 22 December 2017
Available online 25 December 2017

hippocampal activity does not [11,12,18]. Instead, a more robust finding in adults is a relative increase in engagement of the angular gyrus (AG), in the posterior inferior parietal lobe, during arithmetic fact retrieval [11,19–21]. Finally, one study comparing multiplication and subtraction operations in 4th grade children found no differences in either the hippocampus or AG and instead found weak differences in only the primary visual cortex [22].

Because most prior studies have not explicitly examined the proportion of retrieval use, comparisons between arithmetic operations are, at best, an indirect proxy for retrieval-related activity. A more direct approach is to assess strategy use in individual participants within a particular operation, so as not to confound retrieval use and task difficulty. In a strategy assessment, participants are first asked to solve an arithmetic problem, and then are probed on how they computed the answer. This approach has been very successful in studying strategy use – both in adults [17,23] as well as in children [14,15] – and crucially, has been demonstrated to have strong external validity: children who report using retrieval more often than counting strategies also show faster reaction times than children who report relying primarily on counting [24]. Using this approach, Cho and colleagues [6] divided a sample of 7–9 year old children into Retrievers and Counters and, using a multivariate classifier, showed that differences in hippocampal activity patterns could significantly discriminate these groups with an 86% accuracy. Furthermore, a follow-up study revealed that activity levels in the hippocampus were related to individual differences in retrieval use, with higher retrieval use associated with greater hippocampal engagement [5].

To more precisely map the neurodevelopmental trajectory of arithmetic problem solving, Qin and colleagues used longitudinal functional magnetic resonance imaging (fMRI) data to assess the neural correlates of developmental shifts in strategy use during arithmetic problem solving [7]. Specifically, children were assessed twice: initially between 7 and 9 years and then again 1.2 years later. At each of the two time-points, participants underwent a strategy assessment and functional imaging session. Use of retrieval during single-digit addition problem solving increased significantly over the 1.2-year interval, and crucially, was accompanied by increases in hippocampal activity. In contrast, activity in the lateral prefrontal cortex and in the left AG decreased with age. None of these activity changes were, however, correlated with individual differences in changes in retrieval use. Instead, it was increased hippocampal connectivity with prefrontal and parietal cortices that correlated positively with changes in retrieval use. Additional analysis using cross-sectional data revealed that retrieval rates continued to increase in adolescents and adults, but hippocampal activity returned to the same level as children at the first time point. Together these results suggest a developmentally-specific role for the hippocampus in the acquisition of math facts. However, it is not known whether such changes in hippocampal recruitment are the result of maturational changes in this structure during this time period, or whether they reflect experience-dependent effects of formal schooling and instruction.

The main goal of this study was to investigate brain changes that accompany intensive short-term math training in typically developing children. We focused on plasticity of hippocampal response and connectivity building on our previous longitudinal study [7]. An important gap in the literature we address here is that majority of previous retrieval training studies in adults have not found increased hippocampal recruitment and connectivity [19,25,26], (but see Bloechle [27] for an exception). Thus, we investigated whether arithmetic fact learning in children is dependent on hippocampal mechanisms.

We assessed the effects of an 8-week training program designed to improve math skills in nineteen early elementary school-aged children [9,10]. The one-on-one training used a variety of training activities aimed at building conceptual understanding of arithmetic principles and refining strategy use with a particular emphasis on math fact retrieval. In a previous study using the same experimental design, we showed that eight weeks of individual cognitive training not only remediates poor performance in children with math learning disabilities, but also induces widespread changes in brain activity. Neuroplasticity in children with math learning disabilities manifests as normalization of aberrant functional responses in a distributed network of parietal, prefrontal and ventral temporal-occipital areas that support successful numerical problem solving, and is correlated with performance gains [28]. The present study focuses on a larger group of typically developing children who either participated in the training study or served as a control group. Children in the Training group completed an fMRI scanning session in which they verified single-digit addition problems before and after eight weeks of training. During these sessions, we also collected an outside-the-scanner strategy assessment designed to assess changes in strategy use [24]. A no-contact Control group of 15 children completed the fMRI sessions and strategy assessments, but did not take part in the training (Fig. 1A).

We hypothesized that short-term training would alter hippocampal functional responses and connectivity in typically developing children. Furthermore, if behavioral and brain changes observed over development [7] were driven by learning and did not merely reflect brain maturation, we would expect to see similar patterns of changes in short-term training and long-term development. Specifically, we predicted that training would result in (1) behavioral improvements characterized by gains in accuracy, decreases in response times and increases in retrieval strategy-use, (2) increases in hippocampal activity levels, (3) concurrent decreases in prefrontal and parietal activity and (4) increased connectivity of the hippocampus to prefrontal and parietal cortical regions associated with greater use of retrieval strategy use.

2. Methods

2.1. Participants

Participants were 8–9 years of age children in 3rd grade, and were recruited from a wide range of schools in the San Francisco Bay Area using mailings to schools and postings at libraries and community groups. All participants were right-handed and had no history of psychiatric or neurological illness. The initial sample included 46 participants who completed the 8-week math training and the Pre- and Post-training MRI scans. As in our previous studies [7,28,29], all participants had full-scale IQs [30] above 80. Additionally, in contrast to Iuculano et al. [28], we only included children without specific learning disability for math as defined by scores at or above 90 ($>$ 25th percentile) on the Numerical Operation subtest on the Wechsler Individual Achievement Test – Second Edition [WIAT-II, 31], a standardized test of math achievement (see below). Given these criteria, of the total sample of recruited children, one participant was excluded for low IQ and 22 for poor math achievement (WIAT-II scores $<$ 90). Two further participants were excluded for head movement resulting in poor brain image quality (see below). The final sample of the Training group consisted of 19 children (mean age = 8.5, 11 females). All 19 participants maintained compliance and completed the full 8-week training. The initial sample for the no-contact Control group included 28 participants with functional imaging data collected eight weeks apart. Three participants were excluded due to low performance on the Numerical Operations subtest ($<$ 90), 8 were excluded due to poor image quality, and 2 for missing behavioral or imaging data at their Post-training visit, resulting in a final sample of 15 participants (mean age = 8.8, 10 females, see Table 1). Informed consent was obtained from the legal guardian of the child, and study protocols were approved by the Stanford University Institutional Review Board.

2.2. Study overview

Participants in the Training group completed four phases of the study: (i) standardized neuropsychological assessments; (ii) functional

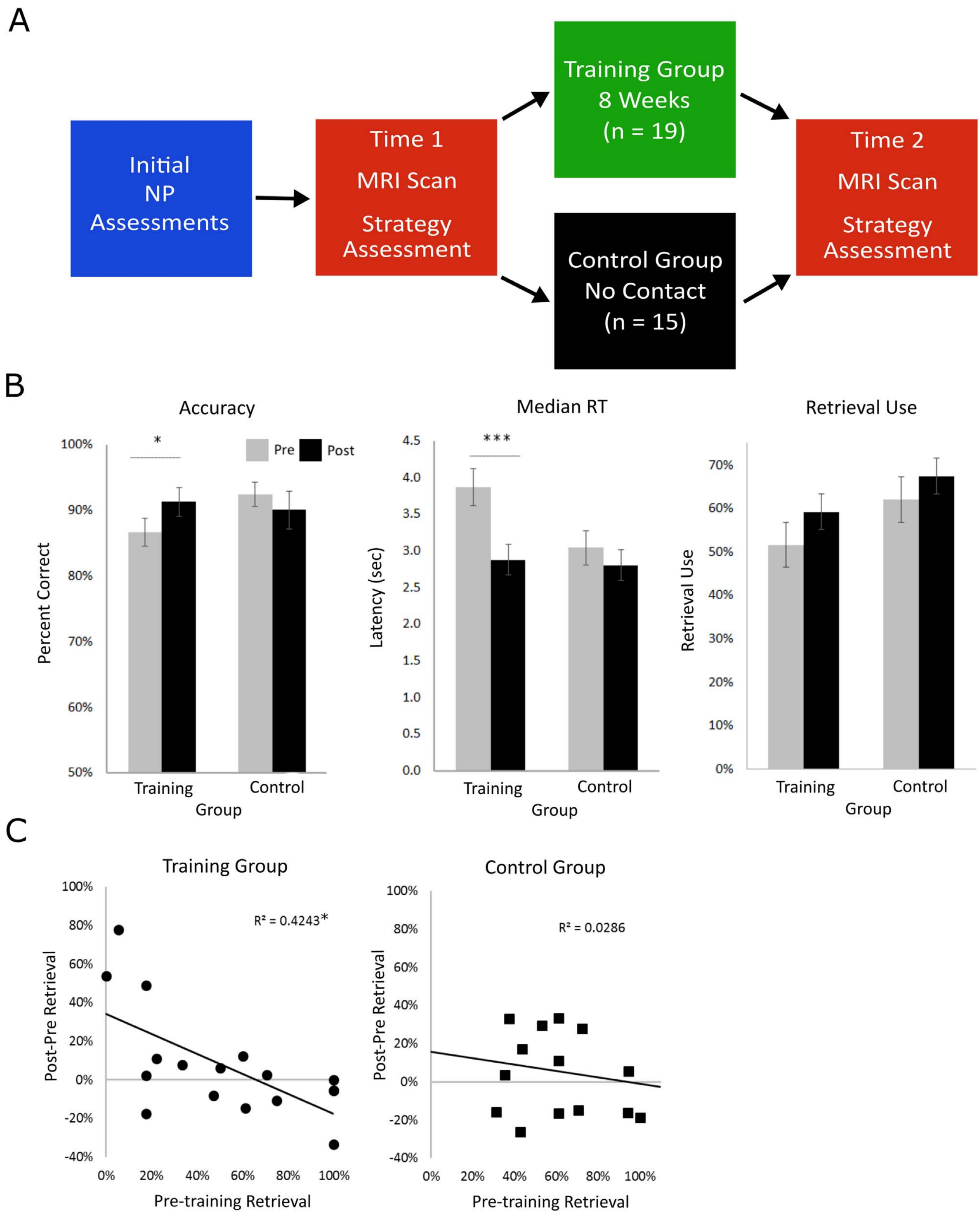

Fig. 1. Overview of training study and behavioral results. (**A**) Participants in the Training group underwent a battery of standardized neuropsychological assessments measuring IQ, reading and math achievement, and working memory (blue box); Time 1 MRI scan and strategy assessment for solving single-digit addition problems (red box); 8-weeks of one-on-one math tutoring (green box); and Time 2 MRI scan and strategy assessment (red box). Participants in the Control group (black box) completed all phases except for the training. (**B**) Children who underwent eight weeks of math training improved significantly in both accuracy (p = .050) and reaction time (p < .001) for the in-scanner arithmetic verification task. Children in the no-contact Control group did not show significant improvements in accuracy (p = .44) or reaction time (p = .26). Between group analysis revealed a marginally significant interaction between group and time for accuracy (p = .064) and a significant interaction for median reaction time (p = .031). Retrieval use during strategy assessment did not increase significantly in either the Training (p = .29) or the Control (p = .36) groups. (C) However, the correlation between percentage of retrieval use at Time 1 and percentage of increase in retrieval use revealed that larger gains in retrieval use were related to lower starting rates in the training group (r = −.65, p =.005), but not in the control group (r = −.17, p = .55). *p < .05, ***p < .001.

Table 1
Participant Demographics and Cognitive Measures.

	Training (n = 19)		Control (n = 15)		
	M	*SD*	*M*	*SD*	*p*
Age (years)	8.5	.5	8.8	.4	.097
Gender	male = 8		male = 5		NA
IQ – WASI					
Verbal	108.9	16.2	114.5	15.8	.314
Performance	108.8	12.6	114.9	16.5	.252
Full scale	110.0	13.1	116.4	15.1	.204
Achievement –WIAT-II					
Numerical operation	107.4	10.5	114.1	14.4	.147
Mathematical reasoning	109.1	10.5	115.7	17.7	.213
Reading comprehension	110.2	11.4	113.5	9.52	.354
Word reading	108.5	9.2	111.9	10.0	.326

WASI = Wechsler Abbreviated Scales of Intelligence, WIAT-II = Wechsler Individual Achievement Test –Second Edition.

brain imaging and outside-the-scanner strategy assessment (Pre-training); (iii) eight weeks of intensive, one-on-one math training; (iv) a second brain imaging session together with a strategy assessment (Post-training). Participants in the no-contact Control group completed all phases except for phase (iii) (see Fig. 1A). The design of the study design is described in detail elsewhere [28].

2.3. Neuropsychological assessments

Participants in the study underwent a comprehensive battery of standardized neuropsychological assessments. Intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence [30]. Academic achievement in mathematics and reading was assessed using WIAT-II [31]. The WIAT-II includes nationally standardized measures of K-12 academic skills and problem-solving abilities, which are normed by grade and time of the academic year (Fall, Spring, or Summer).

2.3.1. Mathematical abilities

WIAT-II includes two measures of mathematics achievement: Numerical Operations and Mathematical Reasoning. Numerical Operations is a paper-and-pencil test that measures number writing and identification, rote counting, number production, and simple addition, subtraction, multiplication, and division problems with single- and double-digit operands. For example, $4 - 2 =$ and $37 + 54$ (presented vertically) are two problems in the 2nd and 3rd grade range. Mathematical Reasoning is a verbal problem-solving test that measures counting, geometric shape identification, and single- and multi-step word problem-solving involving time, money, and measurement with both verbal and visual prompts.

2.3.2. Reading abilities

The WIAT-II was also used to assess reading abilities in order to rule out children with reading difficulties. The Word Reading subtest involves reading individual words presented visually to the child, whereas the Reading Comprehension subtest requires them to match words to pictures and answer questions about sentences and passages they have read [31]. We computed a composite reading score by averaging the two reading measures. All participants, in both groups, had reading composite scores greater than 90 (> 25th percentile).

2.4. Training program

The Training group participated in an 8-week one-on-one training program focused on strengthening conceptual number knowledge and speeded practice on efficient counting strategies for simple addition and subtraction problems [28,32]. This program was adapted from Math Wise [10] and Galaxy Math [33], two math remediation programs that have been previously shown to be effective in school-based studies, particularly for improving performance of children with low math skills. Similar to Math Wise and Galaxy Math, the program involved a total of 15–20 h of training, but was condensed to 8–9 weeks with longer individual lessons. The program consisted of 22 lessons of increasing difficulty and occurred 3 times a week for approximately 40–50 min. See Supekar, et al. [32] and Iuculano, et al. [28] for full details of the protocol.

2.5. Strategy assessment

Arithmetic problem-solving strategies were assessed outside the scanner, immediately upon completion of the brain imaging session. Children answered 24 simple addition problems, while the experimenter recorded the child's reaction time, verbal response, and strategy. The problems involved pairs of integers from 2 to 19, with sums ranging from 6 to 25. The larger operand was equally likely to appear in the first or second position. Ties were not included. Children were asked to solve each problem as quickly as possible, using whatever strategy was easiest for them (e.g., count using their fingers, count in their heads, or retrieve the answer). Immediately after stating the answer, children were asked to report how they solved each problem [24,34]. The experimenter took notes of overt signs of counting, such as finger usage, lip movement, or audible counting, and these were compared against the child's report of how the problem was solved. For each child, we computed the proportion of trials in which retrieval strategies were used. In this analysis we only included the 18 addition problems that involved single digits. There were six single- plus double-digit addition problems (whose sums exceeded 20), which were not covered in the training sessions and therefore excluded from the analysis. Moreover, we excluded trials where no strategy was reported, trials where the assessor disagreed with the child's response, or where the child gave an incorrect answer. Two participants in the Training group did not complete the strategy assessment task due to time limitations. All participants in the Control group completed the strategy assessment. Thus, the final analysis of retrieval use included 17 participants in the training group and 15 in the Control group.

2.6. Neuroimaging

2.6.1. Scanner task

The in-scanner arithmetic verification task consisted of two runs of arithmetic problem solving during which the child verified addition equations (e.g. $3 + 4 = 7$). Problems were presented in a fast event-related fMRI design with 12 single-digit problems per run. In each run, problems were presented horizontally in green lettering on a black background. In half of the problems, the answers presented were correct (e.g. $2 + 4 = 6$) (i.e. valid trials); in the remaining half, the answers presented deviated from the correct solution by $\pm$ 1 or $\pm$ 2 (e.g. $3 + 5 = 7$) (i.e. invalid trials). Arithmetic problems with 1 or 0 as operands were excluded. The larger operand was equally likely to appear in the first or second position. Each trial started with a fixation asterisk that lasted for .5 s. Then, the problem was presented for a maximum of 9.5 s, during which time the child could make their response. The participant used a response box to indicate if the answer was correct or not. After the response, the problem disappeared from the screen and a black screen appeared until the time window was filled to 9.5 s.

A set of 12 non-arithmetic problems was also presented during each run. These problems consisted of number identity verifications (e.g. $7 = 7$) and were randomly interspersed with the arithmetic trials. Invalid trials were counterbalanced as in the arithmetic verification task (i.e. answers deviated from the correct solution by $\pm$ 1 or $\pm$ 2, e.g. $6 = 7$). This condition served as the control for fMRI data analyses in order to better isolate brain activity solely related to arithmetic problem solving, rather than sensory or number processing, decision making and response selection. The task design also included a total of six rest periods — 10 s each —, which occurred at jittered intervals during each run to achieve an optimal event-related fMRI design [35]. The rest periods were not explicitly modeled. Accuracy and median reaction times of correctly solved problems were computed separately for each participant for each condition (i.e. arithmetic verification and number identity verification).

2.6.2. Data acquisition

Brain imaging data were acquired at the Stanford University Lucas Center. Participants in the Training group were scanned on a 3 T GE Signa scanner (General Electric, Milwaukee, WI) using an 8-channel head coil. Participants in the Control group were scanned on a 3 T GE Discovery scanner (General Electric, Milwaukee, WI) using a similar 8-channel coil. The scanning parameters were identical between the groups. Twenty-nine axial slices (4.0 mm thickness, .5 mm skip) were collected parallel to the AC-PC line, using a T2* weighted gradient echo spiral in-out pulse sequence [36] (150 volumes; TR = 2000 ms; TE = 30 ms, flip angle = 80°, 1 interleave). In both groups, scans were acquired with a field of view of 20 × 20 cm and a matrix size of 64 × 64, providing an in-plane spatial resolution of 3.125 mm for a voxel size of 3.125 × 3.125 × 4.0 mm. To reduce blurring and signal loss from field in-homogeneity, an automated high-order shimming method based on spiral acquisitions was used before acquiring the functional MRI scan [37].

High-resolution T1-weighted images were acquired in each child at both scan sessions (i.e. Pre- and Post-training), to improve anatomical co-registration of fMRI maps. A spoiled-gradient-recalled inversion recovery 3D MRI sequence with the following parameters was used: I = 300 ms, TR = 8.4 ms; TE = 1.8 ms; flip angle = 15°; 22 cm field of view; 132 slices in coronal plane; 256 × 192 matrix; 2 NEX, acquired resolution = 1.5 × .9 × 1.1 mm.

2.6.3. fMRI preprocessing

The first 6 volumes were not analyzed to allow for signal equilibration effects. A linear shim correction was applied separately for each slice during reconstruction using a magnetic field map acquired automatically by the pulse sequence at the beginning of the scan [36]. FMRI data were preprocessed and analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Images were realigned to correct for motion, corrected for errors in slice-timing, co-registered to each individual's structural T1 images, spatially transformed to standard stereotaxic space (based on the Montreal Neurologic Institute coordinate system), resampled every 2 mm using sinc interpolation, and smoothed with a 6 mm full-width half maximum Gaussian kernel to decrease spatial noise prior to statistical analysis. For co-registration, the individual's highest quality-rated (either Pre- or Post-) structural MRI sequence was used for both groups. To correct for deviant volumes resulting from spikes in movement, we used de-spiking procedures similar to those implemented in AFNI68. Volumes with movement exceeding .5 voxels (1.5625 mm) or spikes in global signal exceeding 5% were interpolated using adjacent scans. No more than 15% of total volumes per run were repaired in either group. The groups did not differ in terms of movement in any direction (see Supplementary Table S1).

2.6.4. Individual subject and group analyses

Each child completed at least two functional runs of addition and control problems; in some cases, due to excessive movement, up to four extra runs were acquired. Post-hoc run selection was based on the following criteria: (i) total frames interpolated < 20%; and (ii) performance accuracy > 50%. For each participant, the final analyses were performed on the first two available runs meeting the movement and behavioral criteria. Task-related brain activation was identified using the general linear model (GLM) implemented in SPM8. Interpolated volumes flagged at the preprocessing stage were de-weighted. The trials were modeled using a boxcar function convolved with the canonical hemodynamic response function and a temporal dispersion derivative to account for voxel-wise latency differences in hemodynamic response. Low-frequency drifts at each voxel were removed using a high-pass filter (.5 cycles/min). Serial correlations were accounted for by modeling the fMRI time series as a first-degree autoregressive process.

Both correct and incorrect trials were modeled in the GLM in four task conditions: Task Accurate, Control Accurate, Task Inaccurate, and Control Inaccurate. The final voxel-wise contrast and t-statistic maps were generated on the first two sub-conditions only: Task Accurate and Control Accurate. Hence, at a group level, differences in brain activation were compared between Pre- and Post-training sessions contrasting Task Accurate versus Control Accurate conditions. We also examined, at the whole brain level, the relation between change in retrieval strategy rate and brain activation using the same contrast. We corrected for multiple comparisons at the cluster level by using Monte Carlo simulations implemented in Matlab and similar to other studies [6,7,28,38,39]. This method is similar to the AlphaSim procedure implemented in AFNI [40–42]. Ten thousand iterations of random 3D images, with the same resolution and dimensions as the fMRI data, were generated. The resulting images were masked for grey matter and then smoothed with the same 6 mm FWHM Gaussian kernel used to smooth the fMRI data. The maximum cluster size was then computed for each iteration and the probability distribution was estimated across the 10,000 iterations. Based on recent concerns about false positives in fMRI activation [43], significant activation clusters were identified using a height threshold of $p < .005$ and an extent threshold of 87 voxels ($p < .01$) based on a Monte Carlo simulations [38,42].

Functionally defined regions of interest were identified that showed either group-wise changes in activation, or changes related to the changes in retrieval use, in the Training group. Beta values were then extracted from these functional clusters and plotted for both the Training and Control groups. Correlations with changes in retrieval strategy use within each group were compared for significance following Fisher [44].

2.6.5. Functional connectivity analysis

Psychophysiological interaction (PPI) was used to examine the connectivity of the left hippocampus with the rest of the brain during the addition task. PPI analyses measure the temporal relation between a given seed region and all other brain voxels after accounting for the common driving influence of task activity on both the seed and target voxel [45]. Here we used a generalized form of PPI (gPPI) as implemented in the 'Generalized Form of Context-Dependent Psychophysiological Interactions' SPM toolbox [46]. This recently developed method has the flexibility of estimating task-dependent functional connectivity within each task condition, and is therefore especially well-suited for experiments with multiple conditions [47]. A 6 mm sphere, at the peak of the hippocampal functional cluster defined by significant training-contingent effects in the Training group (MNI coordinate: −26, −2, −22), was generated as the seed for the functional connectivity analysis.

At the individual participant level, within each experimental run, we included: (1) four regressors for the psychological variables (i.e. the four task conditions: Task Accurate, Control Accurate, Task Inaccurate, and Control Inaccurate. (2) one regressor for the physiological variable (i.e. the time course in the seed region); and (3) four regressors for the psychophysiological interaction term (i.e. the cross-product of each psychological variable with the seed region time course). Movement parameters (x, y, z, roll, pitch, yaw) and a constant term were also included in the model. Time series for the hippocampus seed were obtained by extracting the first eigenvariate of the raw voxel time series in the ROI, separately for each participant. Changes in connectivity following training were computed by contrasting beta values for Task Accurate – Control Accurate, Pre- vs Post-training.

Contrast images corresponding to PPI effects at the individual-subject level were then entered into a random-effects, group level statistical analysis. The change in the percentage of retrieval-use during the Pre- and Post-training strategy assessment was included as a covariate of interest to determine brain areas in which retrieval fluency was associated with changes in task-dependent functional connectivity of the hippocampus. The search space was restricted to a mask consisting of voxels that showed task-related activation using a liberal height threshold ($p < .05$) on the contrast of Task Accurate vs. Control Accurate combining Pre- and Post-training sessions for the Training group. A liberal threshold was employed to ensure that any task relevant area was included. Significantly activated clusters for the connectivity analyses were again determined using a height threshold of $p < .005$ and cluster extent of $p < .01$, which corresponds to 42 voxels after masking for functional activation. Functionally defined clusters were determined using connectivity contrasts in the Training group. Beta values were then extracted from these clusters and plotted for both the Training and Control groups. Correlation coefficients within each group were compared for significance following Fisher [44].

2.6.6. Effect size computation

Effect sizes for the Pre- vs. Post-training behavioral and brain comparisons were computed using Cohen's *d*. In order to contrast findings with our previous longitudinal study, we also computed Cohen's *d* values for the corresponding analyses from Qin et al. [7]. For behavioral analyses from Qin et al. [7], we report values from the event-related task, which is more comparable to the event-related task used in the current study. Based on the generally accepted practice of categorizing effect sizes into small (.2–.5), medium (.5–.8) and large (.8 and above), we considered effect sizes from the current study as “comparable” to Qin et al. [7] if they fell within or above these ranges.

3. Results

3.1. Behavior

3.1.1. Neuropsychological assessment

Standardized measures of intelligence (verbal, visual and full-scale) and achievement (reading and math) did not differ between the Training and Control groups (see Table 1).

3.1.2. Arithmetic task

Arithmetic performance was assessed in the scanner using a single-digit arithmetic verification task (see Fig. 1B, Supplementary Table S2). Eight weeks of one-on-one training was associated with significant improvements in accuracy ($t = -2.10$, $p = .050$, $d = .50$) and median reaction times ($t = 5.09$ $p < .001$, $d = .98$). As expected, no significant changes were observed in the Control group, for both accuracy ($t = .79$ $p = .44$, $d = .23$) and reaction times ($t = 1.17$, $p = .26$, $d = .25$). Direct comparisons between the groups revealed a marginal interaction between group (Training vs. Control) and time point (Pre- vs. Post-training) for accuracy ($F(1,32) = 3.68$, $p = .064$), which was slightly stronger after accounting for Numerical Operations ($F(1,31) = 4.10$, $p = .051$,) and Math Reasoning ($F(1,31) = 4.17$, $p = .050$) scores. A significant interaction was found for reaction times between group and time point ($F(1,32) = 6.85$, $p = .013$). This interaction remained significant even after controlling for Numerical Operations ($F(1,31) = 4.52$, $p = .042$,) and Math Reasoning ($F(1,31) = 5.80$, $p = .022$) scores. Together, these results indicate that eight weeks of intensive math training produces larger performance gains in arithmetic problem solving than 'schooling as usual'. Moreover, the effect sizes in the Training group are comparable to those observed longitudinally (accuracy $d = .71$; reaction times $d = 1.31$) by Qin and colleagues [7].

3.1.3. Strategy assessment

Next we asked whether behavioral improvements seen in the Training group resulted from increased use of the retrieval strategy when solving arithmetic problems. Use of retrieval strategies did not increase significantly in either the Training ($t = -1.10$, $p = .29$, $d = .24$) or the Control ($t = -.95$ $p = .36$, $d = .21$) groups. These effect sizes are smaller than those observed in the longitudinal sample ($d = .54$). Retrieval use also did not differ significantly between the two groups at either pre- or post-training (all $ps > .31$, $d = .09$). However, the correlation between percent retrieved at Pre and changes in retrieval use with training (Post – Pre) revealed that larger gains in retrieval use were related to lower initial retrieval rates in the Training group ($r = -.65$, $p = .005$), but not in the Control group ($r = -.17$, $p = .55$, see Fig. 1C), although this difference did not reach significance ($Z = 1.54$, $p = .12$). These results suggest that eight weeks of training does not lead to increases in retrieval use in all children, but it is modulated by individual differences in initial retrieval rates.

3.2. Brain imaging

3.2.1. Changes in hippocampal activity associated with short-term training

We first identified brain areas that showed increases in activation following training. Training resulted in significantly greater activation in the left anterior hippocampus (Fig. 2, Table 2). The Control group did

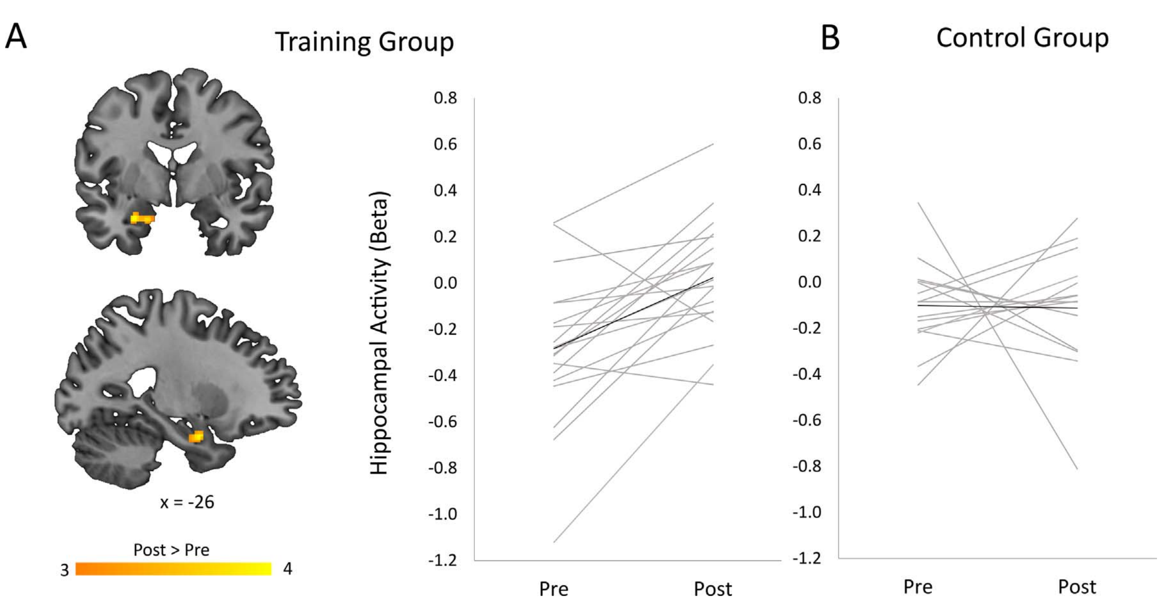

Fig. 2. Training-induced increases in hippocampal activation. (**A**) Left anterior hippocampus region that showed greater activation after eight weeks of training. Increases in anterior hippocampal activation were significant in the Training group ($t = 4.37$, $p < .001$). (**B**) No changes were detected in the Control group ($t = .10$, $p = .92$).

Table 2
Activation changes following 8 weeks of cognitive training (Training Group) or 8 weeks of 'schooling as usual' (Control Group).

Region	Cluster size (voxels)	Peak z-score	Peak MNI Coordinates x	y	z
Training Group					
Post-Pre (Task-Control)					
Left Hippocampus	97	3.52	−26	−2	−22
Pre-Post (Task-Control)					
No significant voxels					
Control Group					
Post-Pre (Task-Control)					
No significant voxels					
Pre-Post (Task-Control)					
No significant voxels					

not exhibit increased brain activity in any brain region (see Table 2). Based on findings from the previous longitudinal study [7], we conducted follow-up ROI analyses in the left hippocampus cluster identified in the Training group (Fig. 2, Table 2). This analysis confirmed significantly greater activation at Post- than at Pre-training (t = 4.37 $p < .001$, d = 1.04) for the Training group, but not for the Control group (t = .10 p = .92, d = .05). An independent samples t-test also showed significantly greater changes in the Training than Control group (t = 2.40, p = .022). This difference remained significant even when controlling for initial differences in accuracy and reaction time ($F(1,33)$ = 4.25, p = .048). These results suggest that short-term training induces significantly greater changes in hippocampal activity than regular schooling. The observed effect sizes in the Training group were within the medium to large range and comparable to those observed in the longitudinal sample (left hippocampus: d = .55; right hippocampus d = .72).

3.2.2. Changes in prefrontal and parietal cortex activity with short-term training

No brain areas showed decreases in activation after short-term training. This pattern contrasts with the longitudinal study [7], which showed decreases in bilateral prefrontal cortex, the right AG and the left superior parietal lobule. For the Control group, no brain areas showed decreased activation (Table 2).

We next examined the relationship between training-induced changes in retrieval strategy use and changes in brain activity associated with arithmetic problem solving. In the Training group, increased retrieval strategy use was associated with decreases in activation of the bilateral AG and the right inferior frontal gyrus (IFG) (Fig. 3). No brain regions showed increases in training-induced activation associated with increased retrieval use. In the Control group, no brain regions were either positively or negatively associated with changes in retrieval use (Table 3). To further explore this pattern of results, we performed ROI analyses to assess differences associated with retrieval use and brain activation between the groups. Direct comparison of the correlation coefficients between groups revealed significant differences in the left AG (Training: $r = -.75$, $p < .001$, Control: r = .48, p = .074; $Z = -3.80$, $p < .001$), the right AG (Training: $r = -.75$, $p < .001$, Control: r = .06, p = .82; $Z = -2.263$, p = .009), and the right IFG (Training $r = -.70$, p = .002, Control: r = .04, p = .89; $Z = -2.31$, p = .021). These results suggest that short-term training induces similar decreases in cortical engagement during arithmetic problem solving as seen in longitudinal samples [7]. Unique to 8-week training, decreases in cortical engagement in regions of the lateral prefrontal and parietal cortices were correlated with individual differences in retrieval use.

3.2.3. Training-induced changes in retrieval strategy use are correlated with increased hippocampal-parietal connectivity

We next examined hippocampal connectivity changes associated with individual changes in retrieval strategy use. Training-induced increases in retrieval use were correlated with significant increases in hippocampal connectivity with the right intraparietal sulcus (IPS, Fig. 4, Table 4). Follow-up ROI-based correlation analyses revealed that this effect was significant in the Training group (r = .67, p = .003), but not in the Control group (r = .34, p = .22), although the direct comparison of slopes did not reach statistical significance in this case (Z = 1.16, p = .25). Nevertheless, the relationship between changes in connectivity and changes in retrieval use in the training group were comparable to those reported in a previous longitudinal sample (r = .59) [7].

4. Discussion

The present study is the first to investigate whether short-term training alters brain responses and connectivity in typically developing children, and whether these changes recapitulate long-term longitudinal developmental changes observed across a time period of a year or more [7]. Specifically, we asked if an intensive, 8-week cognitive training program aimed at strengthening arithmetic problem-solving [33] mirrors longitudinal changes in behavior, brain response and connectivity associated with the development of arithmetic problem solving skills over the course of a year [7]. We found that eight weeks of intensive arithmetic training resulted in (1) improvements in accuracy and reaction time; (2) increased hippocampal activity; (3) decreased lateral prefrontal and parietal activity associated with increased retrieval rates; and (4) increases in hippocampal-parietal cortical connectivity associated with increased retrieval rates. In contrast, eight weeks of regular educational experiences ('schooling as usual', here conceptualized as a no-contact control group) did not produce any of these patterns of changes in behavior, brain responses or brain connectivity. We discuss below the detailed findings and their implications for math cognition and learning and we highlight the potential of contrasting results from longitudinal and training studies as a way to elucidate fundamental brain changes accompanying academic skill acquisition over multiple time periods.

4.1. Short-term training recapitulates longitudinal changes in behavioral performance

Early elementary school is a period of rapid acquisition and mastery of arithmetic knowledge, marked by improvements in accuracy and latency [3,48]. Reaction time improvements associated with training (d = .98) were comparable to the effects observed over a 1.2-year interval (d = 1.31) [7] and much stronger than following eight weeks of standard educational experience (d = .25). For accuracy, gains were comparable between the Training group (d = .50) and the longitudinal group (d = .71). In contrast, very modest gains were seen after eight weeks of 'schooling as usual' (d = .23). Together these results indicate that short-term intensive one-on-one training can induce substantial improvements in behavior, that are comparable to changes accompanying education experiences over an interval seven times longer (i.e. 1.2 years).

4.2. Short-term training did not increase retrieval strategy-use

Behavioral improvements in arithmetic skills during early elementary school are often driven by shifts from effortful counting strategies towards more efficient memory-based retrieval strategies [2]. In a previous longitudinal study spanning over one year, Qin et al. [7] reported increases in retrieval use with medium effect sizes (i.e. d = .54). In the current study, retrieval increases were more modest in both Training (d = .24) and Control (d = .21) groups. However, in the

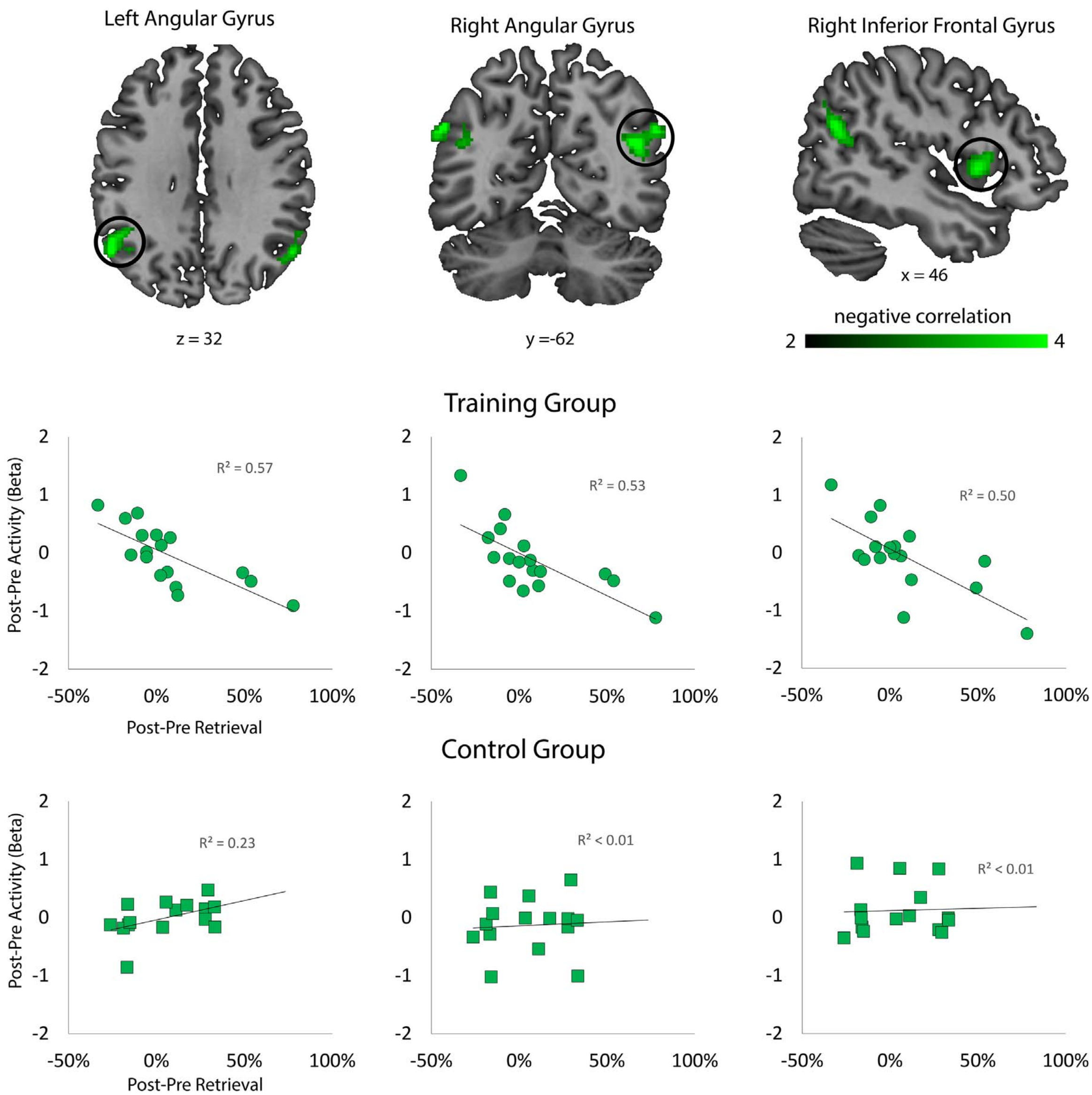

Fig. 3. Prefrontal and parietal activation decreases with increased use of retrieval strategies after training. Bilateral angular gyrus and right inferior frontal gyrus showed significant negative correlations between training-induced changes in brain activity and retrieval use in the Training group (all *ps* $\leq$ .002), but not in the Control group (all correlations positive and *ps* > .07).

Table 3
Activation changes correlating with increases in retrieval use following 8 weeks of cognitive training (Training Group) or 8 weeks of 'schooling as usual' (Control Group).

Region	Cluster size (voxels)	Peak z-score	Peak MNI Coordinates x	y	z
Training Group					
Post-Pre (Task-Control)					
No significant voxels					
Pre-Post (Task-Control)					
Left Angular Gyrus	288	3.45	−54	−62	32
Right Angular Gyrus	280	3.39	44	−62	24
Right Inferior Frontal Gyrus	174	3.26	46	10	2
Control Group					
Post-Pre (Task-Control)					
No significant voxels					
Pre-Post (Task-Control)					
No significant voxels					

Training group, significant changes in retrieval use were evident as a function of initial retrieval rates (Fig. 1B). Specifically, children with lower initial retrieval rates made larger gains following eight weeks of training (Fig. 1C). This suggests that more time (or more practice) is needed to make gains in this measure at the higher end of the distribution. Nonetheless, these results are encouraging as they suggest that short-term training can be most helpful for children with the lowests rates of memory-based strategy-use.

4.3. Short-term training recapitulates longitudinal changes in hippocampal activity

Short-term training resulted in increased activity in the left hippocampus, and no such effect was detected in the Control group. This result demonstrates the specificity of our findings with respect to intensive training. The effect size in the Training group (d = 1.04) was comparable with longitudinal increases previously observed in a 1.2-year period, in the left (d = .55) and in the right (d = .72) hippocampus [7]. These results add to the growing body of cross-sectional

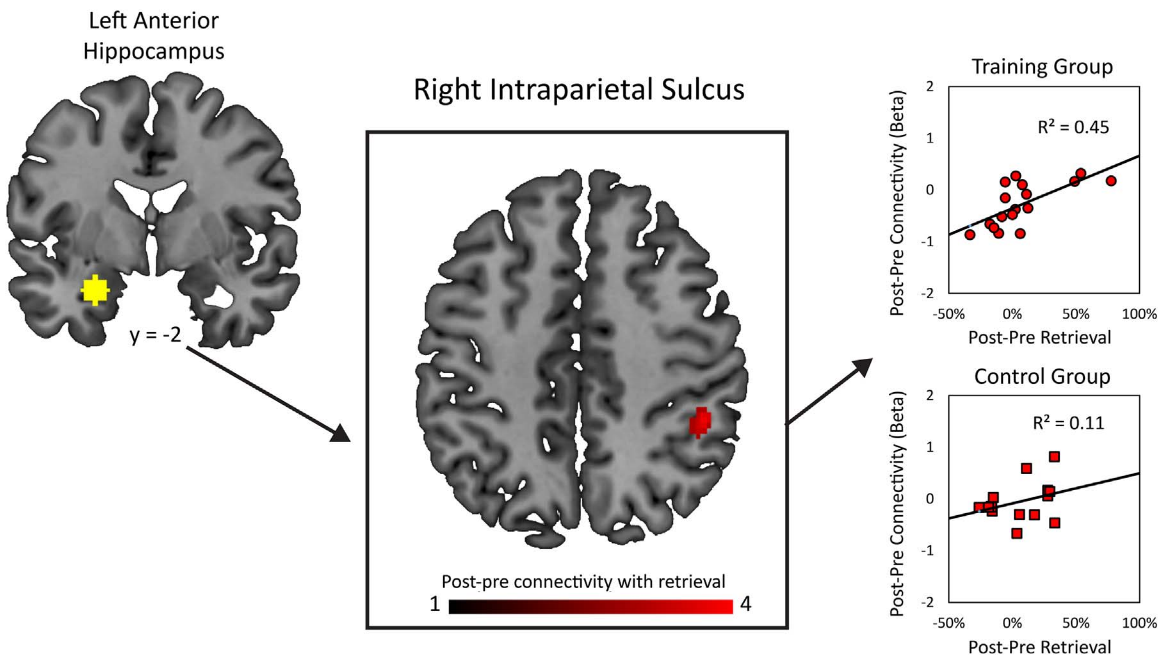

Fig. 4. Hippocampal connectivity increases with training were correlated with changes in retrieval strategy use. Increased retrieval use after eight weeks of training was associated with significant increases in connectivity of left anterior hippocampus with right intraparietal sulcus (r = .67, p = .003). The control group did not show such a relation (r = .34, p = .22).

Table 4
Hippocampal functional connectivity changes correlating with increases in retrieval use following 8 weeks of cognitive training (Training Group) or 8 weeks of 'schooling as usual' (Control Group).

Region	Cluster size (voxels)	Peak z-score	Peak MNI Coordinates x	y	z
Training Group					
Post-Pre (Task-Control)					
Right Intraparietal Sulcus	62	3.85	46	−40	46
Pre-Post (Task-Control)					
No significant voxels					
Post-Pre (Task-Control)					
Control Group					
No significant voxels					
Pre-Post (Task-Control)					
No significant voxels					

data implicating the hippocampus in the acquisition of math fact knowledge during early elementary school years. Two recent neuroimaging studies comparing addition and subtraction problems, operations that are thought to differ in their rates of retrieval use, both found greater hippocampal activity during addition than subtraction [8,16]. Moreover, using a correlational design, Cho, et al. [5] examined the relationship between strategy use and brain responses associated with arithmetic problem solving in a large sample (N = 78) of 2nd and 3rd grade children. Consistent with the current results and those of Qin et al. [7], greater use of retrieval was also associated with greater hippocampal activity.

The hippocampus is known to play an essential role in learning and memory, specifically in the binding of new information together [49–51]. In the context of arithmetic, the associative learning properties of the hippocampus may be involved in connecting operands to answers. An influential theory of hippocampal function posits that hippocampal engagement is required for the learning of new information and for building schema knowledge [52]. Yet, when schemas are established, the hippocampus is no longer needed to acquire new information, as long as the information is consistent with the schema. On the one hand, this proposal may help explain the lack of hippocampal activity reported when adults are solving problems using retrieval [11,18,20,21] or even when learning to memorize new problems [19,25,53]. In this view, adults have a well-established schema for arithmetic which no longer requires hippocampus engagement, even for solving newly memorized problems [19]. In contrast, children are still in the process of developing schematic knowledge, and therefore rely more on the hippocampus when learning math facts.

On the other hand, several recent findings appear to challenge a model of hippocampus-independent math learning in adults. Qin and colleagues found refinements in multivariate patterns of activity in the hippocampus in adolescence and adulthood, even without significant hippocampal activity over baseline [7]. Training studies in adults have compared neural responses for trained and untrained problems after training, to elicit activity patterns for problems solved by retrieval vs. calculation [19]. Recently, Bloechle and colleagues expanded on this design by scanning participants before and after training on complex multiplication facts. They found greater hippocampal activity for trained, relative to untrained, facts in adults [27]. Klein and colleagues [54] also found hippocampal activity using parametric analyses in several single time point arithmetic tasks in adults. Together these results suggest that the hippocampus may be involved in successful retrieval of math facts in both adults and children. Future studies should employ pre/post training designs to help disentangle the specific role of the hippocampus at different developmental stages and differing task demands.

4.4. Short-term learning-related decreases in engagement of prefrontal and parietal cortex

Training was also associated with decreases in activity related to gains in retrieval use. Specifically, larger increases in retrieval were correlated with greater decreases in activity in the right prefrontal cortex and in the bilateral AG. Children in the Control group, who did not undergo training during the 8-week period, did not display decreases in fronto-parietal cortex activity, nor changes in their brain response associated with retrieval use. This finding contrasts with previous longitudinal results, which found decreases in lateral prefrontal and parietal cortex for almost all participants [7]. In the current study, we did not find decreases in the Training group as a whole. Rather, individuals who showed the largest decreases in fronto-parietal cortex activity also showed the largest increases in retrieval use. Importantly, these results suggest that brain changes following eight weeks of intensive training are less pronounced and that a longer time is needed to achieve decreases in fronto-parietal cortical activity in all children.

Consistent with the general pattern reported in Qin et al. [7], we found decreases in AG activity following eight weeks of intensive training, albeit correlated with changes in retrieval use. Our findings of AG decreases are especially interesting given the putative role of this region in math fact retrieval in adults [19,20,55]. Studies contrasting retrieval rates, either by self-report [20,21], arithmetic operations [11], or training history [19] suggest the AG is more active when answers are retrieved rather than calculated. But this interpretation has been challenged by findings demonstrating that differences in AG activity seem to result from differences in deactivation, rather than activation [18,24]. This pattern is consistent with evidence pointing to the AG as a node of the default mode network [56,57]. Confirming this interpretation is recent work by Bloechle and colleagues [27], showing that greater deactivation for untrained problems drives AG differences between trained and untrained problems, rather than increases in activity for trained problems.

Our results are in line with previous longitudinal findings [7] and suggest that increasing mastery of math problem solving is accompanied by decreased lateral prefrontal and parietal activity. This convergence between longitudinal and training studies contrast with findings from cross-sectional studies [5,6]. For example, Cho et al. [5], found that greater use of retrieval strategies was correlated with *greater* lateral prefrontal and AG activity. An implicit assumption in individual differences research is that children with differing skill levels can be thought of as occupying differing positions along a learning trajectory. The divergence between cross-sectional and longitudinal findings challenge this assumption and illustrate that only multi-time point, within-subjects designs, can truly uncover individual trajectories of brain changes accompanying learning.

4.5. Short-term training recapitulates longitudinal changes in hippocampal connectivity

Following eight weeks of one-on-one training, we found increases in connectivity between the left hippocampus and the right IPS that were related to increases in retrieval use. This result is consistent with previous longitudinal developmental findings [7], which also reports hippocampal connectivity changes related to changes in retrieval rates over a 1.2-year time interval. Consistent with the current results of strengthening contralateral hippocampal-parietal connectivity, Qin et al. reported increased connectivity between right hippocampus and left IPS. Notably in both studies, increases in connectivity accompanied activity decreases in nearby parietal regions (left superior parietal in Qin et al., right AG in the current study). Intriguingly, intrinsic connectivity of the IPS to the hippocampus also increased following this same training program [29]. In that study, a bilateral IPS ROI had increased connectivity with the left hippocampus, albeit more posterior than the cluster identified here. Recent animal studies report that silencing the CA3 area of the left hippocampus impaired associative memory, while the equivalent manipulation in the right hippocampus did not [58]. These results suggest that the left hippocampus might produce the strongest changes in an associative learning task, such as ours, particularly after short-term training.

An important difference with previous longitudinal studies is that changes in hippocampal-cortical connectivity associated with eight weeks of training were less pronounced and more localized than following a year of longitudinal change. Specifically, Qin et al. [7], found increased hippocampal-prefrontal, as well as hippocampal-parietal connectivity related to increases in retrieval use. In contrast, eight weeks of training did not uncover connectivity changes in hippocampal-prefrontal circuits. These results suggest that reorganization of connectivity changes between the hippocampus and prefrontal cortex associated with math learning might occur over longer time periods, and might be related to the fact that the prefrontal cortex matures more slowly than the parietal cortex [59–61].

4.6. Disentangling the effects of experience and maturation of brain development during academic skill learning

A fundamental goal of developmental cognitive neuroscience is to understand the brain mechanisms associated with successful learning. Cross-sectional designs can identify neural signatures of proficient performers, but cannot map individual learning trajectories. Longitudinal studies provide essential knowledge about the typical course of behavioral improvements and brain plasticity changes both in terms of functional activation and connectivity. However, changes observed in longitudinal studies over longer time intervals cannot be attributed definitively to educational experiences rather than ongoing brain maturation. Moreover, linking brain changes to classroom learning experiences is especially difficult in the United States where educational practices vary widely across schools, even within circumscribed geographic regions.

Training studies are uniquely positioned to address these issues. First, training studies can track individual trajectories of brain and behavioral change across different groups of subjects. Second, short time frames such as the eight-week training period used in the present study, minimize the effects of ongoing brain maturation. Finally, training studies with well-characterized curricula can more directly link education experience to brain changes. By using appropriate control groups and conditions, training studies can properly assess the causal role of learning on brain activity and connectivity. The no-contact control group employed here enabled us to determine the effects of intense training relative to ‘schooling as usual’. Further work with a larger group of participants, using identical tasks and randomized assignment of participants are needed for more direct comparisons between groups and across different time-scales of learning and skill development. Moreover, contrasting distinct education programs between training groups can further increase relevance for educational practice, by probing the effect of specific learning experiences.

Cross-sectional, training, and longitudinal designs each provide complementary pieces of the puzzle in establishing the brain-basis of academic learning and achievement. When results diverge between experimental designs – as in the case of prefrontal and parietal activity patterns reported here – it becomes necessary to reexamine underlying assumptions and design follow-up experiments to reconcile these results. Crucially, when findings from individual differences analysis, long-term longitudinal changes and short-term training-induced plasticity all converge – as we found here for the hippocampus activation and connectivity – confidence in the functional role of a region in learning and cognitive skill acquisition process is bolstered. The next step is to build on this knowledge and design new training programs to more effectively engage target brain regions and further advance our understanding of the neurobiological mechanisms of learning.

5. Conclusion

We elucidated mechanisms of cognitive skill acquisition by characterizing changes in brain response and connectivity that accompany eight weeks of intensive one-on-one training. Crucially, we found remarkable correspondence between the effects of short-term training and long-term developmental changes observed over a 1.2-year interval [7]. By showing that these changes were specific to the Training group and were not evident in the Control group, we were able to characterize hippocampus-mediated mechanisms of activity and connectivity underlying specific learning experiences over an 8-week period. As such, these results further solidify the importance of the hippocampus in the acquisition of mathematical knowledge. More generally, the present study demonstrates the utility of training studies to investigate causal relationships between learning experiences and brain plasticity, setting the stage for using cognitive neuroscience approaches to refine instructional practice and promote learning in every child.

Acknowledgements

This work was supported by NIH grants to Vinod Menon (HD047520 and HD059205) and Miriam Rosenberg-Lee (MH101394) and NWO grant to Dietsje Jolles (446-12-001). We thank Katie Cheng for assistance with data analysis.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.tine.2017.12.001.

References

[1] D.C. Geary, Cognitive predictors of achievement growth in mathematics: a 5-year longitudinal study, Dev. Psychol. 47 (6) (2011) 1539–1552.
[2] Z. Chen, R.S. Siegler, II. Overlapping Waves Theory Monographs of the Society for Research in Child Development, vol. 65(2), 2000, pp. 7–11.
[3] D.C. Geary, Children's mathematical development: Research and practical applications, in: Proceedings of the Rochester Symposium on Developmental Psychopathology, American Psychological Association, Washington, DC, US, vol. 5, 1994.
[4] B. Butterworth, The Mathematical Brain, Macmillan, London, 1999.
[5] S. Cho, et al., Hippocampal-prefrontal engagement and dynamic causal interactions in the maturation of children's fact retrieval, J. Cogn. Neurosci. 24 (9) (2012) 1849–1866.
[6] S. Cho, et al., How does a child solve 7 + 8? Decoding brain activity patterns associated with counting and retrieval strategies, Dev. Sci. 14 (5) (2011) 989–1001.
[7] S.Z. Qin, et al., Hippocampal-neocortical functional reorganization underlies children's cognitive development, Nat. Neurosci. 17 (9) (2014) 1263–1269.
[8] B. De Smedt, I.D. Holloway, D. Ansari, Effects of problem size and arithmetic operation on brain activation during calculation in children with varying levels of arithmetical fluency, Neuroimage 57 (3) (2011) 771–781.
[9] L.S. Fuchs, et al., Remediating computational deficits at third grade: a randomized field trial, J. Res. Educ. Eff. 1 (1) (2008) 2–32.
[10] L.S. Fuchs, et al., Remediating number combination and word problem deficits Among students with mathematics difficulties: a randomized control trial, J. Educ. Psychol. 101 (3) (2009) 561–576.
[11] K.M. Lee, Cortical areas differentially involved in multiplication and subtraction: a functional magnetic imaging study with a case of selective acalculia, Ann. Neurol. 48 (2000) 657–661.
[12] R. Kawashima, et al., A functional MRI study of simple arithmetic - a comparison between children and adults, Cogn. Brain Res. 18 (3) (2004) 227–233.
[13] N. Hayashi, et al., Regional differences in cerebral blood flow during recitation of the multiplication table and actual calculation: a positron emission tomography study, J. Neurol. Sci. 176 (2) (2000) 102–108.
[14] P. Barrouillet, R. Lepine, Working memory and children's use of retrieval to solve addition problems, J. Exp. Child Psychol. 91 (3) (2005) 183–204.
[15] P. Barrouillet, M. Mignon, C. Thevenot, Strategies in subtraction problem solving in children, J. Exp. Child Psychol. 99 (4) (2008) 233–251.
[16] M. Rosenberg-Lee, et al., Brain hyper-connectivity and operation-specific deficits during arithmetic problem solving in children with developmental dyscalculia, Dev. Sci. 18 (3) (2015) 351–372.
[17] J.I.D. Campbell, Q. Xue, Cognitive arithmetic across cultures, J. Exp. Psychol.-General. 130 (2) (2001) 299–315.
[18] M. Rosenberg-Lee, et al., Functional dissociations between four basic arithmetic operations in the human posterior parietal cortex: a cytoarchitectonic mapping study, Neuropsychologia 49 (9) (2011) 2592–2608.
[19] M. Delazer, et al., Learning complex arithmetic - an fMRI study, Cogn. Brain Res. 18 (1) (2003) 76–88.
[20] R.H. Grabner, et al., To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving, Neuropsychologia 47 (2) (2009) 604–608.
[21] N. Tschentscher, O. Hauk, How are things adding up? Neural differences between arithmetic operations are due to general problem solving strategies, Neuroimage 92 (2014) 369–380.
[22] B. Polspoel, et al., Strategy over operation: neural activation in subtraction and multiplication during fact retrieval and procedural strategy use in children, Hum. Brain Mapp. 38 (9) (2017) 4657–4670.
[23] J.I.D. Campbell, J.C. Timm, Adults' strategy choices for simple addition: effects of retrieval interference, Psychon. Bull. Rev. 7 (4) (2000) 692–699.
[24] S.S. Wu, et al., Standardized assessment of strategy use and working memory in early mental arithmetic performance, Dev. Neuropsychol. 33 (3) (2008) 365–393.
[25] M. Delazer, et al., Learning by strategies and learning by drill - evidence from an fMRI study, Neuroimage 25 (3) (2005) 838–849.
[26] A. Ischebeck, et al., Imaging early practice effects in arithmetic, Neuroimage 36 (3) (2007) 993–1003.
[27] J. Bloechle, et al., Fact learning in complex arithmetic-the role of the angular gyrus revisited, Hum. Brain Mapp. (2016).
[28] T. Iuculano, et al., Cognitive tutoring induces widespread neuroplasticity and remediates brain function in children with mathematical learning disabilities, Nat. Commun. 6 (2015) 8453.
[29] D. Jolles, et al., Reconfiguration of parietal circuits with cognitive tutoring in elementary school children, Cortex 83 (2016) 231–245.
[30] D. Wechsler, Wechsler Abbreviated Scale of Intelligence, The Psychological Corporation, San Antonio, TX, 1999.
[31] D. Wechsler, The Wechsler Individual Achievement Test — Second Edition (WIAT-II), The Psychological Corporation, San Antonio, TX, 2001.
[32] K. Supekar, et al., Neural predictors of individual differences in response to math tutoring in primary-grade school children, Proc. Natl. Acad. Sci. USA 110 (20) (2013) 8230–8235.
[33] L.S. Fuchs, et al., Effects of first-grade number knowledge tutoring with contrasting forms of practice, J. Educ. Psychol. 105 (1) (2013) 58–77.
[34] R.S. Siegler, The perils of averaging data over strategies: an example from children's addition, J. Exp. Psychol.: General. 116 (3) (1987) 250–264.
[35] M.H. Kao, et al., Multi-objective optimal experimental designs for event-related fMRI studies, Neuroimage 44 (3) (2009) 849–856.
[36] G.H. Glover, S. Lai, Self-navigated spiral fMRI: interleaved versus single-shot, Magn. Reson. Med. 39 (3) (1998) 361–368.
[37] D.H. Kim, et al., Regularized higher-order in vivo shimming, Magn. Reson. Med. 48 (4) (2002) 715–722.
[38] M. Rosenberg-Lee, M. Barth, V. Menon, What difference does a year of schooling make? Maturation of brain response and connectivity between 2nd and 3rd grades during arithmetic problem solving, Neuroimage 57 (3) (2011) 796–808.
[39] T. Iuculano, et al., Brain organization underlying superior mathematical abilities in children with autism, Biol. Psychiatry 75 (3) (2014) 223–230.
[40] T. Nichols, S. Hayasaka, Controlling the familywise error rate in functional neuroimaging: a comparative review, Stat. Methods Med. Res. 12 (5) (2003) 419–446.
[41] B.D. Ward, Simultaneous Inference for FMRI Data. AFNI 3dDeconvolve Documentation, Medical College of Wisconsin, Milwaukee, WI, 2000.
[42] S.D. Forman, et al., Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold, Magn. Reson. Med. 33 (5) (1995) 636–647.
[43] A. Eklund, T.E. Nichols, H. Knutsson, Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates, Proc. Natl. Acad. Sci. USA 113 (28) (2016) 7900–7905.
[44] R.A. Fisher, On the probable error of a coefficient of Correlation deduced from a small sample, Metron 1 (1921) 3–32.
[45] K.J. Friston, et al., Psychophysiological and modulatory interactions in neuroimaging, Neuroimage 6 (3) (1997) 218–229.
[46] D.G. McLaren, et al., A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches, Neuroimage 61 (4) (2012) 1277–1286.
[47] J.M. Cisler, K. Bush, J.S. Steele, A comparison of statistical methods for detecting context-modulated functional connectivity in fMRI, Neuroimage (2013).
[48] N.C. Jordan, L.B. Hanich, D. Kaplan, A longitudinal study of mathematical competencies in children with specific mathematics difficulties versus children with comorbid mathematics and reading difficulties, Child Dev. 74 (3) (2003) 834–850.
[49] J.L. McClelland, B.L. McNaughton, R.C. Oreilly, Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory, Psychol. Rev. 102 (3) (1995) 419–457.
[50] L. Davachi, Item, context and relational episodic encoding in humans, Curr. Opin. Neurobiol. 16 (6) (2006) 693–700.
[51] H. Eichenbaum, Hippocampus: cognitive processes and neural representations that underlie declarative memory, Neuron 44 (1) (2004) 109–120.
[52] S.H. Wang, R.G.M. Morris, Hippocampal-neocortical interactions in memory formation, consolidation, and reconsolidation, Annu. Rev. Psychol. 61 (2010) 49–79.
[53] L. Zamarian, A. Ischebeck, M. Delazer, Neuroscience of learning arithmetic-Evidence from brain imaging studies, Neurosci. Biobehav. Rev. 33 (6) (2009) 909–925.
[54] E. Klein, et al., Considering structural connectivity in the triple code model of numerical cognition: differential connectivity for magnitude processing and arithmetic facts, Brain Struct. Funct. 221 (2) (2016) 979–995.
[55] S. Dehaene, et al., Three parietal circuits for number processing, Cogn. Neuropsychol. 20 (3–6) (2003) 487–506.
[56] M.D. Greicius, et al., Functional connectivity in the resting brain: a network analysis of the default mode hypothesis, Proc. Natl. Acad. Sci. USA 100 (1) (2003) 253–258.
[57] M.E. Raichle, et al., A default mode of brain function, Proc. Natl. Acad. Sci. USA 98 (2) (2001) 676–682.
[58] O.A. Shipton, et al., Left-right dissociation of hippocampal memory processes in mice, Proc. Natl. Acad. Sci. USA 111 (42) (2014) 15238–15243.
[59] J.N. Giedd, et al., Quantitative magnetic resonance imaging of human brain development: ages 4–18, Cereb. Cortex 6 (4) (1996) 551–560.
[60] C.K. Tamnes, et al., Development of the cerebral cortex across adolescence: a multisample study of inter-related longitudinal changes in cortical volume, surface area, and thickness, J. Neurosci. 37 (12) (2017) 3402–3412.
[61] G. Ziegler, et al., Multivariate dynamical modelling of structural change during development, Neuroimage 147 (2017) 746–762.